REMARKS

Status of the Claims

Claims 1, 3 to 9, 21, 22 and 25 to 27 were pending. Claim 21 has been amended as shown above to remove the term "derived from." Thus, claims 1, 3 to 9, 21, 22 and 25 to 27 are pending as shown above.

35 U.S.C. §103

Claims 1, 3-9, 21, 22 and 27 were again rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,521,066 (hereinafter "Menzel") in view of U.S. Patent No. 5,348,867 (hereinafter "Georgiou"). (Office Action, pages 2-5).

Menzel was again cited for disclosing a transmembrane fusion protein comprising a ligand binding domain, a cytoplasmic toxR NDA binding region, a hydrophobic ToxR transmembrane region and a reporter gene operably linked to the ctx operon. *Id.* Menzel was further alleged to disclose that binding a ligand to the ligand binding domain induces a conformational change in the cytoplasmic domain, which in turn induces binding to the promoter region of the reporter gene. *Id.* It was also alleged that Menzel discloses that ligand binding domains and dimerization domains are interchangeable and that Menzel discloses the ligand binding domain can be anything capable of forming a dimer. *Id.* at page 3. While the Office Action states that Menzel does not explicitly disclose use of antibodies on the bacterial surfaces, it was alleged that it would have been obvious to use Georgiou's heterologous scFV antibodies in Menzel's fusion proteins. *Id.*

It was also alleged that Menzel's disclosure of the cytoplasmic domain of the toxR fusion protein acts as a transducer and this meets the requirements of the instant claims with respect to this element. *Id.*

Claim Construction

As a threshold matter, Applicants again note that the Examiner has improperly construed various claim terms.

As set forth in *Phillips v. AWH* (Fed. Cir. 2005, en banc), 75 USPQ2d 1321 and MPEP § 2110.01, construction of any claim term must begin with the claims themselves. According to Philips, and to a wealth of prior case law[1], "the ordinary and customary meaning of a claim term is the meaning that term would have to a person of ordinary skill in the art in question at the time of the invention." *Id.*. Simply put, "the inquiry into how a person of ordinary skill in the art understands a claim term provides an objective baseline from which to begin claim interpretation." *Id.*.

In the instant case, it is clear that the plain meaning of the terms "ligand-binding domain" and "transducer" would be understood by one of skill in the art from the claims to exclude Menzel's system. The term "ligand-binding domain" and "dimerization domain" are among those used in the art to describe different types of binding domains. As is well-known to molecular biologists, the term "dimerization domain" refers to a protein that interacts with another protein, either via direct interactions of dimerization domains or, alternatively, via the binding to two proteins to the same ligand (via the proteins ligand binding domain). This is clearly set forth in Menzel (see, Menzel, col. 4, lines 32-37):

> The terms "dimerization domain" and "region capable of forming a dimer" refer to a polypeptide sequence capable of forming a self-dimer, either spontaneously or as the result of ligand binding and the like. Exemplary dimerization domains may be derived from trkC, GCN4, the HSV scaffold protein ICP35, HIV integrase, and the like.

On the other hand, the term "ligand binding domain" is understood by the skilled artisan to denote a domain that binds to a single different molecule. Dimerization via the ligand binding domain is clearly neither required not encompassed by this term. The plain meaning of this term is not that of a dimer made up of three molecules (i.e., ligand-binding domain of protein#1—ligand—ligand binding domain of protein#2), but of a two-molecule structure of ligand-binding domain and a ligand.

Likewise, the term "transducer" is clearly understood by the skilled artisan in the context of the claims to be separate from both the intracellular domain and the responsive element. In

[1] For example, *Vitronics Corp. v. Conceptronic, Inc.* 90 F.3d 1576 (Fed. Cir. 1996); *Innova/Pure Water, Inc. v. Safari Water Filtration Systems, Inc.* 381 F.3d 1111 (Fed. Cir. 2004)

the claims, the transducer is clearly a different molecule than the intracellular domain. By contrast, Menzel teaches that the intracellular domain acts directly on the promoter region of the reporter gene.

Thus, the plain and customary meaning of the term "ligand-binding domain" to the skilled artisan clearly refers to domain that binds to and is activated by a single, specific ligand, not to ligand-mediated dimerization. Similarly, the term "transducer" clearly refers to a molecule separate from both the intracellular domain (which activates it) and the responsive element (which it activates). Accordingly, the pending claims, when properly construed, are entirely different than Menzel's dimerization systems which do not contain a transducer.

Thus, as approved by the Federal Circuit in *Phillips*, the contexts in which the terms "ligand-binding domain" and "transducer" are used in the claims are entirely consistent with its plain meaning to one of skill in the art. In particular, independent claim 1 clearly requires that upon binding of its specific ligand, the ligand-binding domain alone activates an intracellular enzymatic signal transforming domain. In turn, the activated intracellular domain activates a separate transducer, which transducer, when activated, then acts on the responsive element of the reporter. By contrast, binding of a ligand is not sufficient in Menzel's system – the ligand must then mediate dimerization. Moreover, Menzel's intracellular domain acts directly on the reporter gene promoter – there is no separate transducer as plainly required by the claims.

As further set forth in *Phillips,* "the claims, of course, do not stand alone. Rather, they are part of a 'fully integrated written instrument' [citing *Markman*]. For that reason, claims 'must be read in view of the specification, of which they are a part.' " *Phillips,* at page 1336. Nonetheless, the court in *Phillips* restates the axiom that only in cases in which the specification contains a "special definition given to the claim term ... that differs from the meaning it would otherwise possess" can the plain and customary meaning as determined from the claim language be overridden. *Id.*

Here, the as-filed specification clearly defines a ligand-binding domain as it would be understood by the skilled artisan, namely a ligand-binding domain that is activated upon binding of the ligand and does not require ligand-mediated dimerization to be active. See, e.g., page 15, lines 1 to 7 of the as-filed specification):

> Substances which may be identified by the present invention include, but are not limited to, proteins, peptides, sugars, fatty acids, ions, microorganisms, including

> bacteria, viruses, parasites and fungi. Accordingly, the ligand-binding domain may be an antibody, an antibody fragment, cellular receptor or any other ligand-binding protein, such as Staphylococcus Proteins A and G, a macrophage Fc receptor, a carbohydrate moiety, or an ion-binding moiety, such as domains from sodium or potassium channels.

Similarly, the as-filed specification plainly defines the transducer as a separate molecule from the intracellular domain (signal transforming domain) (see, e.g., page 16, lines 11 to 15 of the as-filed specification):

> The transducer is activated by the signal converting element upon ligand binding. The transducer may be any molecule that can recognize and to a change in conformation, electrical charge, addition or subtraction of any chemical subgroup, such as phosphorylation, glycosylation, and in turn is capable of triggering a detectable response.

Therefore, as would be understood by the skilled artisan, the specification's definitions are entirely consistent with the plain and customary meaning of the terms "ligand-binding domain" and "transducer."

The Federal Circuit in *Phillips* has also reiterated that the prosecution history, like the specification and claims themselves, is part of the "intrinsic evidence" and, accordingly, provides evidence of how the inventor understood the claims. *Phillips* at page 1337.

Here, the Examiner has improperly ignored the fact that the prosecution history establishes that Applicants understood the term "ligand binding domain" to mean a domain activated by binding of a single, specific ligand (not via dimerization) and a "transducer" to be separate from the intracellular (signal converting domain). Specifically, Applicants have repeatedly noted such in their Responses.

In sum, when the claims are construed properly, it is clear that they do not encompass an extracellular dimizeration domain or an intracellular domain that acts as a transducer.

Menzel and Georgiou do not render the properly construed claims obvious

To briefly reiterate, claims 1, 3-9, 21, and 27 are directed to biodetectors comprising three elements: (1) a transmembrane fusion protein having an extracellular antibody domain and an intracellular enzymatic signal transforming domain which is activated upon binding of a selected substance to the antibody; (2) a transducer which is activated by the activated

intracellular enzymatic signal domain of the transmembrane fusion protein; and (3) a transcription activation element that is activated by the active form of the transducer, to give a detectable signal. Claim 22 is directed to a genetically engineered bacterial cell comprising such a biodetector. Menzel and Georgiou fail to teach or suggest these claimed elements.

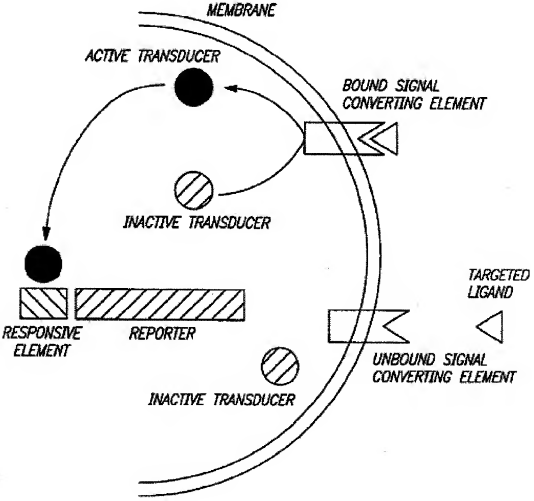
1. Menzel only detects dimerization

Menzel pertains to a toxR-ctx system for detection of **dimerization** of a toxR fusion protein. As noted above, in all cases, dimerization must occur for Menzel's system to function. In particular, ToxR is a transmembrane protein containing a DNA binding domain at its N-terminus. Dimerization of toxR modulates the ability of the N-terminus of toxR to bind to the ctx promoter and initiate transcription. See Menzel, *e.g.*, at col. 1, lines 33-36; col. 2, lines 3-6; and col. 4, lines 15-17. See also claim 5, which recites a process for detecting dimer formation of the toxR fusion protein.

In contrast, the biodetector of the appealed claims detects binding of a single substance (a ligand) by its binding to an extracellular antibody domain, which triggers a cascade resulting in a detectable signal.

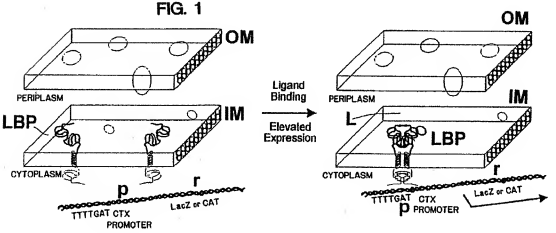
2. The toxR-ctx system of Menzel has no intracellular enzymatic signal domain

Furthermore, as reiterated above, the claimed biodetectors require that a transducer be activated by the activated intracellular domain. In turn, the transducer then activates the reporter. Therefore, there are at least 3 necessary components to active the reporter in the claimed system – extracellular domain, intracellular domain and transducer (see, FIG. 2 of the specification):



By contrast, Menzel's system completely lacks a transducer as claimed. Rather, the cytoplasmic (intracellular) domain of the Menzel's transmembrane protein acts directly on the promoter when the ligand is bound to the extracellular (ligand binding) domain (FIG. 1 of Menzel):

FIG. 1



Thus, the instant claims are drawn to systems having 3 separate components and, moreover, clearly specify which component activates the responsive element to produce a detectable signal. Menzel lacks the claimed transducer component entirely and as such does not in any way teach or suggest a biodetector in which the extracellular domain is an antibody which binds to a ligand and in which binding of the ligand triggers (via a cascade) expression of the reporter gene, as claimed.

Because this component of the claimed biosensor is entirely lacking in the system described by Menzel (which relies solely on dimerization of toxR with no transducer whatsoever), Menzel does not teach or suggest all the elements of the claims.

3. The toxR-ctx system of Menzel has no extracellular antibody domain

As repeatedly noted, Menzel does not describe or suggest using an extracellular antibody domain for detecting substances through ligand binding. Antibodies that bind a particular substance can be readily generated by one of ordinary skill in the art by eliciting an immune response to the substance or by production recombinantly. Thus, an advantage of the present system is that a wide variety of selected substances can be detected with biosensors as claimed that use antibody domains for ligand binding (see specification, *e.g.*, at page 12, lines 4-9; and page 15, lines 1-4). In contrast, the system of Menzel only detects substances that are capable of modulating dimerization of a toxR fusion protein.

The Examiner's repeated contention that certain antibody classes (*e.g.*, IgA) can form dimers that could be used in Menzel's system (see Office Action, page 3) is incorrect. As previously noted, and reiterated above, in all cases, Menzel requires that, when present, the ligand mediate dimerization. Menzel does not simply detect a conformational change in toxR, but rather, the dimerization of toxR, which is required for toxR to associate with the ctx operon to activate expression of a reporter gene (see Menzel, *e.g.*, at col. 1, lines 33-36; col. 2, lines 3-6; and col. 4, lines 15-17). This completely different than both the claimed invention and dimerization of naturally-occurring IgA. Therefore, Menzel **teaches away** from any system in which dimerization itself is not modulated by the substance that is to be detected. In contrast, the instant claims detect ligand binding to an antibody domain, not dimerization of an antibody.

Furthermore, absolutely no evidence has been presented in support of the assertion that, at the time of filing, IgA monomers (or dimers) expressed as part of a transmembrane fusion protein would actually form dimers (or polymers). To support this rejection, the Examiner must show that, as of the filing date, it was routine to create fusion proteins that spanned a membrane and in which the extracellular domain of IgA monomers (or dimers) bound to other IgA monomers (or dimers) so as to activate the intracellular portion of the transmembrane fusion protein.

The rejection is based on an incorrect claim construction (ligand-binding domain is a dimerization domain) and completely unsupported assertions about IgA dimers. Thus, it is clear that the rejection cannot stand.

4. Georgiou fails to fill the gaps of Menzel

The secondary reference of Georgiou fails to make up for the deficiencies of Menzel. Georgiou relates to methods for expressing proteins on the surface of bacterial cells by using a tripartite chimeric gene having a membrane targeting sequence, a sequence encoding a transmembrane segment, and a sequence encoding a selected protein of interest. Although Georgiou describes expression of single-chain antibodies using this method, as the Examiner asserts (Advisory Action, page 5), Georgiou fails to describe or suggest any method for detecting a selected substance bound to an antibody on the surface of a bacterial cell. In particular, Georgiou fails to describe or suggest any intracellular enzymatic signal domain for transducing a

signal to a transcription activation element. Thus, neither Georgiou nor Menzel, alone or in combination, describe or suggest a recited element of the claims.

For the reasons of record, Menzel and Georgiou do not teach or suggest the claimed elements. There is nothing whatsoever in either reference about ligand-binding domains and transducers as claimed and, accordingly, no combination of Menzel and Georgiou that would result in the claimed biodetectors. Thus, the rejection should be withdrawn.

35 U.S.C. § 112, 1st paragraph, written description

Claims 1, 3-9, 21-22 and 25-27 were newly rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not adequately described by the as-filed specification. (Office Action, pages 5-8). In particular, it was alleged that the claims encompass "limitless combination of transmembrane fusion proteins" and that only the exemplified biodetectors are described.

Applicants strongly traverse the rejection and supporting remarks

The written description requirement is satisfied when the as-filed specification, in light of the knowledge possessed by the skilled artisan at the time of filing, reasonably conveys that Applicants were in possession of the claimed subject matter, in this case a biodetector including an extracellular antibody domain, an intracellular enzymatic domain, a transducer and a reporter gene. *See, e.g., In re Lukach*, 169 USPQ 795, 796 (CCPA 1971); *In re Lange*, 209 USPQ 288 (CCPA 1981).

In the instant case, it was well known at the time of filing that antibodies expressed as fusion protein would bind to their selected ligand. This is in contrast to the Examiner's unsupported assertion that IgA monomers (or dimers) would be functional in this way. The specification is replete with disclosure regarding antibody domains and their expression in bacterial cells and representative examples of such antibody domains. See, page 15, lines 8-18 and Examples. Signal transforming domains were also well known in the art at the time of filing and described on pages 15-16 of the specification. It is axiomatic that a specification does not need to re-describe what is well known and based on the ample disclosure in the specification, the skilled artisan would clearly recognize that Applicants were in possession of the claimed biodetectors and withdrawal of the rejection is in order.

35 U.S.C. § 112, 2nd paragraph

Claim 21 was newly rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite for reciting "derived from PhoQ." (Office Action, page 8).

The foregoing amendment to claim 21 obviates the rejection.

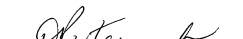
CONCLUSION

Applicants respectfully submit that the claims in condition for allowance.

If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

Date: April 23, 2009

By: 

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